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INTRODUCTION

Hazards from environmental contaminants have become a necessary part of life in industrial countries. In the past

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16. ABSTRACT Hazards from environmental contaminants have become a necessary part of life in industrial countries. In the past few decades, a number of "new" problems have arisen [termiticide-treated premises, reentry into pesticide-treated fields, acid rain, aldicarb in ground water, dioxins in city environs, military use of dioxin-contaminated herbicides, accidents with PCB's and PBB's and other persistent chemicals, a large number of potentially hazardous chemicals in dump sites, and other problems which have caused public awareness of environmental contamination]. These compounds are often found in small amounts (parts per billion), and the potential hazard has often been inadequately clarified. Although most industrial countries share the problem with the U.S., this latter country seems especially vulnerable due both to the sheer quantity of production and the lack of proper perspectives and management following World War II.

A major change in assessment of contamination has been the realization that the skin is not the important barrier to penetration once believed. This route of entry is now more carefully considered in regulatory activities, although it is perhaps less important than gastrointestinal and respiratory routes of entry. It has recently been suggested that both contaminated and drinking waters may be important routes of skin entry of organic compounds. It seems appropriate to consider any route as potentially important, the hazard depending upon both the chemical and the particular set of circumstances which affect intake. ...

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few decades, a number of "new" problems have arisen [termiticide-treated premises, reentry into pesticide-treated fields, acid rain, aldicarb in ground water, dioxins in city environs, military use of dioxin-contaminated herbicides, accidents with PCB's[1] and PBB's and other persistent chemicals, a large number of potentially hazardous chemicals in dump sites, and other problems which have caused public awareness of environmental contamination]. These compounds are often found in small amounts (parts per billion), and the potential hazard has often been inadequately clarified. Although most industrial countries share the problem with the U.S., this latter country seems especially vulnerable due both to the sheer quantity of production and the lack of proper perspective and management following World War II.

A major change in assessment of contamination has been the realization that the skin is not the important barrier to penetration once believed. This route of entry is now more carefully considered in regulatory activities, although it is perhaps less important than gastrointestinal and respiratory routes of entry. It has recently been suggested (1) that both contaminated and drinking waters may be important routes of skin entry of organic compounds. It seems appropriate to consider any route as potentially important, the hazard depending upon both the chemical and the particular set of circumstances which affect intake. Although acute exposure may be of importance in limited situations, chronic exposure is of greatest concern.

This review will not address the work on pesticides covered by Brooks in 1975 (2). However, some of the earlier work on dermal penetration in mammals will be discussed, as important concepts in this rapidly-changing field may be

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[1]ABBREVIATIONS

BP for benzo(a)pyrene; DFP for diisopropyl fluorophosphate; HBN for hexabromonapthalene; MCA for 3-methylcholanthrene; PAH for polycyclic hydrocarbons;PBB for polybrominated biphenyls; PBP for polybromonitrobiphenyls; PCB for polychlorinated biphenyls; PNA for p-nitroaniline; TBBC for thio bis(6-t-butyl-m-cresol); TCDD for 2,3,7,8-tetrachlorodibenzo-p-dioxin; TCDF for tetrachlorodibenzofuran; Tris for tris(2,3-dibromo propyl)phosphate.

unfamiliar to environmental toxicologists who are not involved in dermatological studies. A number of reviews and texts have appeared in recent years which provide valuable insights, particularly those derived from drug examples (3-9). Commercial products have been appropriately discussed (10). The effects of oil pollution is a specialized subject and has been recently reviewed (10a) as well as a review on aquatic toxicology (10c).

The literature on pulmonary uptake has purposefully been omitted from the discussion because of the specialized technology of that field of endeavor. Reviews of interest include 11-15. Newly emerging problems caused by volatile compounds in hazardous waste dumps, termiticiding etc. must now be added to the difficulties inherent in studies of automobile and industrial exhaust hazards, an already overburdened area of research.

METHODOLOGY

Dermal

Two primary methods have evolved for studying dermal penetration *in vivo*. In the indirect method (16), the radioactive compound is applied to the desired skin area (frequently human volunteers), and the appearance of radioactivity in the urine is followed for a five-day period. To correct for incomplete excretion the subject is given an injected dose of the compound and the radioactivity determined in the urine over the same period. The percent absorption is determined as:

$$\% \text{ absorbed} = \frac{\% \text{ urinary radioactivity, topical}}{\% \text{ urinary radioactivity, parenteral}} \times 100$$

In the direct method (17,18), radioactive compound is applied to experimental animals which are killed at selected time intervals. Radioactivity remaining at the site of application is assumed to be the unpenetrated fraction, although skin-bound radioactivity and volatility are factors that cause some uncertainty. As such experiments are usually conducted in metabolism cages, recovery of radioactivity from urine, feces, CO_2, and other tissues can be easily determined at each time interval, permitting an account of the total

radioactivity applied (19). Another desirable feature of this method is availability of fractions for the assessment of metabolism.

When the two methods of measuring penetration (direct and indirect) were compared, a close correlation between the methods was found, especially after the second day of sampling (20).

Appearance of applied material in blood is a positive indication of penetration, but the dynamic situation is soon confused in vivo by the appearance of unknown metabolites and sequestering to tissues (21,22). Other less-used dermal methods include an audioradiological method (23) and the method of Fredriksson (24) in which a back monitor follows absorption of high intensity gamma emittors as they leave the site of application.

A noninvasive method for determining dermal absorption has recently been described (25) using optical properties which measure changes in a voltage output related to cutaneous microcirculation. This inovative method shows much promise for studies on man, but the method must await further experimentation.

Gastrointestinal

Gastrointestinal absorption in vivo has been neglected as a means of determining penetration. Most research has involved feeding trials instead of applying a known amount to the stomach. The gastrointestinal absorption of a number of metallic compounds, as well as others, has been recently reviewed (26). In tests utilizing known amounts, radioactive compound is applied with a stomach needle, and previously starved animals killed at selected intervals (27). The gastrointestine is removed and the contents washed; collected radioactivity is assumed to be the nonpenetrating dose. The method allows analysis of fluids and tissues, but adherence to the wall of the gastrointestine may cause uncertainty. The stomach and intestine may be ligated to ascertain contribution from these two areas separately (28). A more direct method has been described by Pekas (29,30) where a fistalateral blood vessel is operatively attached to a collecting device which permits a direct measure of absorption.

In Vitro

The use of in vitro techniques as a useful correlation to in vivo techniques has been suggested by Franz (31) who found an 80% correlation between the results of in vivo and in vitro experiments. Bronaugh (32,33) confirmed this hypothesis with a more direct study and found good correlations between compounds of widely differing penetration rates (Fig. 1). Following application, radioactivity is determined in the bathing media of static or flow-through systems. The in vitro method with human skin (31) shows the greatest potential for meaningful correlations, and a unique trap has been devised with this method for cases in which volatility becomes an important factor (34,35). The use of artificial membranes (36) has had limited utilization.

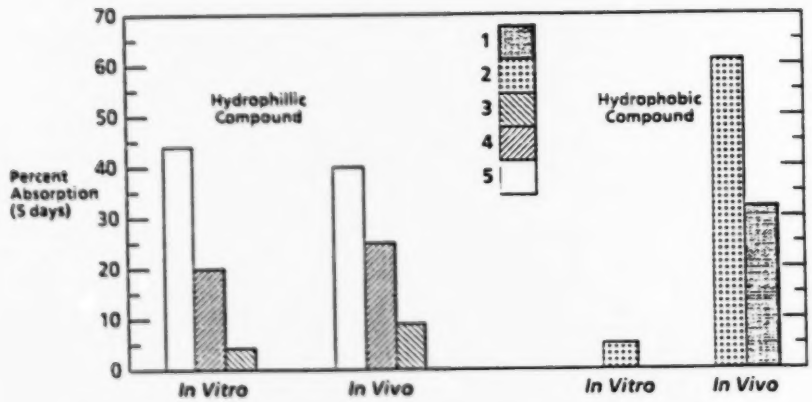

Figure 1. Correlation of in vitro and in vivo absorption in rats (modified from 32,33). 1. 1-(3-ethyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-napthalenyl)-ethanione; 2. 3-phenyl-2-propenyl-2-amino benzoate. 3. urea. 4. acetyl salicylic acid. 5. benzoic acid.

Treatment

Most investigators prefer to conduct research with animals shaved at least 24 hours previously. This introduces an experimental problem, and only one paper has addressed the possible differences in penetration between shaved and unshaved animals (37). In this case no significant difference was noted. The use of hairless mice has been suggested (38) and human skin has been grafted to mice (39). Development of methods utilizing porcine skin flaps which ensure normal vasculature for subsequent *in vitro* perfusion experiments have recently shown promise (40).

Solvent

A question in methodology concerns the vehicle in which the toxicant is introduced. Vehicles are legion, and a few examples include acetone (19), water (41), petrolatum (32), emulphor (27), wettable powder (19), DSMO (42) and ethanol (38). There is no "best" solvent, as all (even water) would be expected to alter the skin in some fashion. It is particularly difficult to compare a number of compounds with different solubility characteristics. The use of water-based formulations seems desirable but two problems are manifest. The detergent or co-solvent has some effect on membranes, and the slow loss of the solvent causes problems with animal-holding procedures. EPA guidelines (43) suggest a "normal" vehicle in water solution.

Skin Washing

Washing of the site of application may show the surprising result of enhanced absorption (6,44); so oft-publicized decontamination procedures may actually worsen the hazard.

Biotransformation During Penetration

Although cutaneous biotransformations have been known for some time (45), the importance of skin metabolism in toxicology has only recently been recognized (46). As cancer of the skin is an important form of malignant neoplasm, studies to assess the capacity of skin to metabolize xenobiotics are of utmost importance. For example, it was recently shown that MCA induced metabolism of BP by 19-fold in

adult rat skin and 10-fold in neonatal rat skin (47). Holland et al. (48) have shown that BP does not penetrate skin until some metabolism is effected. While enzymic activity in skin appears to be low, 2-6% of hepatic values (49), under certain conditions (apparently favored by slow entry) metabolism could be important in certain circumstances. At the extreme, it has been shown that 100% of benzoyl peroxide is metabolized to benzoic acid during in vitro metabolism of human skin (50).

ANIMAL STUDIES

Introduction

The reader is directed to Klaassen (51) for a discussion of the anatomical and other factors which affect penetration of dermal and oral treatments. Summaries of specialized studies on neonatal skin (52) and of basic skin function with regard to penetration (53) have recently appeared.

Humans. Due to studies of dermatology and the importance of human subject experimentation in that field, a number of recent review articles and books have appeared (see above) that impact in the area of environmental contaminants. It is of interest to note that when some dermal agents are used over a period of time (e.g., topically applied mecurials), elevated amounts of metals may appear in tissues (54). Although with drug examples, different vehicles are usually used for application and the chemicals tend to be more water soluble, the information gained is of great importance in cases involving non-drug examples. A number of studies with environmental contaminants (mostly dermal) have been made with humans, as shown in Table 1. This summary includes only environmental contaminants (drug and efficacy tests excluded) and only those studies giving percent penetration or other absorption parameters.

These studies show that human skin is seldom an important barrier to penetration. The compounds represent a wide array of chemical and physical properties and show a wide range of penetrability. Although some compounds are poorly absorbed dermally [such as paraquat in humans (144)], a combination of gross carelessness and dermatological conditions may still

result in untoward tragic consequences (145). Even the sterile conditions of surgery may permit absorption of potential toxicants such as methyl methacrylate through surgeon's gloves (146).

Laboratory Animals. A number of studies with other animals are also summarized in Table 1. As with humans, skin is seldom an important deterrent to penetration. For those compounds with great acute toxicity (such as parathion), effects are quickly manifested. Even where absorption is more limited (as in percutaneous absorption of aflatoxin [88]) chronic effects may became important over time. It should be noted (76) that the results of dermal penetration of five insecticides in animals of diverse phyla were not as generally believed (103). Penetration through the insect cuticle is often much slower than higher organisms, contrary to the concept frequently stated in the literature, a belief which is difficult to reverse.

Skin appears to be more of a barrier to hydrophilic compounds (such as maleic hydrazide or captan, 41), and this group of chemicals is probably less hazardous for that reason. Exceptions may include such highly water soluble compounds as nicotine, which also has marked lipid solubility, increasing its absorptive potential (19). Metals are often lacking in the ability to penetrate through the skin (63), but their stability makes them important contaminants despite their low absorptivity. There are a number of exceptions to this generalization, and conversion to organic metal complexes enhances absorption appreciately. Penetration of plutonium via the intestine may be of importance (63a).

Correlation with Physical Parameters

Although older literature suggests meaningful correlations with such physical properties as partition coefficients, water solubility, size of molecule, etc., a number of recent studies have failed to show consistent correlations. Although many examples could be chosen, a recent report (19) with 14 toxicants of widely differing chemical and physical properties demonstrates that no consistent correlation between any physical factor and penetration is evident. It is particularly

frustrating to attempt correlations using compounds of very similar properties (such as highly lipid-soluble pyrethroids, fenvalerate and permethrin) and find their penetration rates are markedly different (19,41). Viscosity has recently been reported to be correlate with penetration rates (99). In a study of half-time penetration and benzene solubility of a group of steroids (100a), a number of outliers caused the model to lack significance. Whereas the model illustrates the importance of physical and chemical features, a significant number of outliers failed to fit the model. This suggests that correlation of physical constants and penetration should not be regarded too highly until confirmed.

Gastrointestinal Absorption

Reports of investigations of gastrointestinal absorption have been more limited than those of dermal experiments. This is somewhat surprising as the oral route in penetration is important due to ingestion of xenobiotics associated with food. Table 1 shows recent data from these limited tests. Some features should be highlighted. Although gastrointestinal absorption would be expected to be more effective because of the increased surface area afforded by intestinal villi, experiments with the same compounds dermally (19) and orally (27) were surprisingly similar. In the case of permethrin, penetration was fastest for the dermal and slowest for the gastrointestinal route. It is an axiom that penetration by the stomach is normally much less than that by the intestine, largely because of a limited residence time. If compounds are permitted greater residency times in the stomach (as in ligation experiments) the stomach could become an important route of entry (28).

A review of the ingestion of asbestos fibers (101), suggests that a small fraction of ingested asbestos penetrates the gastrointestinal mucosa. It was concluded that there was low probability for increased risk of cancer by this route. The contribution of lead in dust seems strongly correlated to habits of children (particularly in urban situations) from ingesting contaminated particles (dust-hand-mouth) (102). Large molecules, such as botulina toxin, are primarily absorbed through the small intestine (102a).

Protective Clothing

An appreciable amount of research has been conducted regarding protective clothing for pesticide exposure (131). Whereas clean clothing of suitable manufacture may help reduce hazard, problems are manifest because it is difficult to force laborers to wear suitably treated clothing, and re-use of clothing (108) and even protective gloves (132) are important factors in added hazard for workers. Recent studies have suggested protective clothing as part of a protective garment kit supplied by the manufacturer when applicators purchase particularly hazardous pesticides (133).

Occlusion

The obvious parameter of more rapid entry if the skin is injured needs no discussion, but the less obvious problem of skin occlusion is not well-known. A covering over the treated area permits more rapid entry both because that area of the skin differs physiologically and wipe-off and evaporation of the treated skin is retarded (100). In one study the exposure of infants to nursery linens containing small amounts of pentachlorophenol was found to be the source of poisoning (141).

Pesticide Resistance as a Result of Retarded Penetration

Among the mechanisms for resistance to pesticides (134), insect strains have been discovered that absorb appreciably less toxicant (135). Experiments to define the mechanisms have shown that qualitative differences, but not quantitative differences, are manifest among the cuticular phospholipids of resistant and susceptible strains (136). In other studies (137), both qualitative and quantitative differences were found.

"Best" Animal Model for Absorption Studies

It is obviously beneficial to find animal models that most clearly correlate with humans. A number of such studies have been made through the years, and Fig. 2 summarizes the most recent experiments. Other rodents (data not shown) are least likely to mimic humans (19) whereas primates show the highest

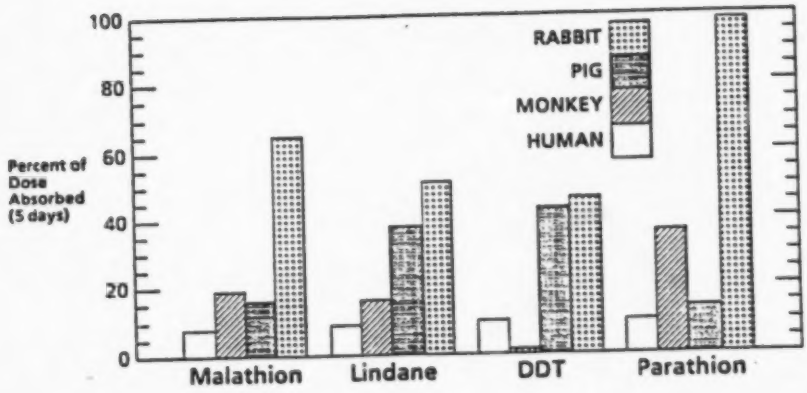

Figure 2. Absorption of selected pesticides *in vivo* by different animal species (modified from 4,20).

correlation. The miniature pig is intermediate but more closely resembles the human case than do rodents.

In Vivo vs In Vitro Absorption

Although correlation of *in vivo* and *in vitro* data with humans shows much promise (31,32) some problems have emerged. The vascularization of the dermis in the *in vitro* situations is much different than *in vivo* and the use of surfactants to enable extraction from the dermis may introduce appreciable uncertainty (33).

Site of Application

The anatomical site of application versus absorption is summarized in Table 2. Absorption is slower through the more protected areas (palmer and plantar for example) while penetration is relatively rapid on what might be considered as high exposure areas (face, neck, and upper back). Penetration is fastest through the genital area.

SOME RECENT PROBLEMS

Several potentially important new environmental problems

have been recognized in recent years regarding dermal exposure. Whereas direct exposure of applicators to pesticides has been recognized as the most important hazard, the problem of worker reentry into fields previously treated with pesticides has only recently been recognized. Over 200 cases of reentry poisoning have been reported since 1975 from a labor force of approximately 200,000 per year although few cases have been adequately authenticated.

Reentry

The problem has been discussed in two comprehensive reviews (104,105). California appears to report the greatest incidence despite similar geography, weather, and agricultural practices in Texas, New Mexico and Arizona. The United States Environmental Protection Agency (106) has published national reentry restrictions which suggest that the problem is regional. Experiments with heavily-treated crops in the eastern US (107,108) failed to define reentry as an important hazard, barring gross disregard for worker safety. Reentry regulations in California are much stricter than other states, and their legislation requires comprehensive research for all pesticides (109). Whereas any attempt to reduce hazards to workers is commendable, many pesticides lack suitable testing procedures (no clear-cut parameter of toxicity as is the case with cholinesterase inhibitors). Thus, regulations may create problems of registration but do not necessarily provide meaninful solutions to the reentry hazards of all pesticides. Work in California (109a-117), Washington (118), Arizona (119), North Carolina (120-122), Florida (123), and Texas (124) have defined a number of important characteristics such as dislodgable residues, measures of worker exposures, protective clothing, monitoring of cholinesterase inhibition, worker habits, experiments to estimate reentry periods, modeling, etc. Although three comprehensive efforts (121,115,111) have been made to follow the protocol of Milby (104) to establish reentry periods, for a variety of reasons none have been successful, illustrating the difficulty of this type of research. One interesting aspect of research in this area concerns the considerable experimental-administrative effort required for human subjects research. The use of human

subjects is highly desirable, but the ethical and administrative problems essentially preclude this desirable feature for most investigations. For example, a significant proportion of the production of certain fruits, such as strawberries, is harvested by teenagers, many 15 years old or younger, and it has been suggested that this is a different exposure problem to that of older workers. However, the great difficulty in comparing young human workers with older groups has caused a gap in our knowledge. Two studies (17,75) have attempted to clarify the problem by using young and old experimental animals.

Only one fatal episode has been reported. In this instance a person was permitted to enter a parathion-treated tobacco field immediately after treatment (123a). Circumstances surrounding the large number of non-fatal poisonings are often not factually reported. For example, one major reentry episode in California was ultimately traced to migrant laborers spending the night in a previously-treated orchard (124a). Dusty conditions, limited rainfall, high levels of application, and optimal oxidation conditions for conversion to the P=O metabolite seem to be major contributing factors to the unique problems of California (104).

Neuropathy

A second recent problem occurred with an insecticide, leptophos, which is known to cause delayed neuropathy. Although banned for sale in the U.S., it was sold in large quantities to combat cotton insects in Egypt. Either following dermal exposure or contaminated water holes, a large number of water buffalo manifested nerve symptoms (125). The exposure and symptomology of humans was not so well-identified, but it is estimated that 3000 humans were affected and 30 deaths resulted (126). A large volume of literature exists on mechanisms of injury, and investigations in chickens, the experimental model of choice, showed rapid uptake of the chemical (127).

Poor Production Practices

A problem resulting from poor production techniques has been reported in certain under-developed countries. Whereas

rather pure pesticides were offered for sale from developed countries, as patent rights expired less qualified manufacturers produced pesticides with measurable impurities. In Pakistan (128) some 7500 workers were made ill as a result of isomalathion contamination from malathion production. The problem was quickly identified (129) and production practices either altered or chemicals purchased from uncontaminated supplies (130).

Miscellaneous

Attempts have been made to formulate pesticides with special clays or polymers which cause the pesticide to be released more slowly and hence have less dermal hazard. In simulated reentry tests with mice (138), less hazard was noted with the controlled-release formulation. The formulation causes a minor environmental problem with honey bees because controlled-release particles may be transported intact to the hive (139). Certain target organisms, such as fire ants, are able to sieve the particles upon intake and hence show that penetration characteristics should not be adhered too rigidly.

SUMMARY

Toxic waste dumps, contamination of potable water, industrial accidents, treatment of houses for pests, and countless other exposures to potentially hazardous chemicals have become a major issue during the past several decades. Whereas major legislation, such as the Toxic Substances Act, is an important step in solving future problems, many of the problems were initated one-half or more centuries ago and appreciable funds and time will both be required to effect satisfactory solutions.

Until fairly recently, the main portals of entry for hazardous substances were judged to be the respiratory and oral routes. It has now been shown that the dermal route is also an important avenue for many poisons. As chronic, not acute, toxicity is accepted as the major health hazard, constant exposure to small quantities of multi-chemicals as a necessary component of everyday life is an issue requiring greater attention.

Whereas partition coefficients and other physical parameters may be used as broad generalizations regarding entry, it has become apparent that these factors are often overused for specific cases. The illusive simple factor explaining absorption has thus far escaped identification.

The use of adequate animal models has only recently been considered of key importance. It seems obvious that small rodents are poor predictors of human absorption, and use of better human predictors is recommended. Obviously, routine tests with rodents will be used initially, but more specialized tests require appropriate animal models. Many chemicals may be tested on humans *per se* but suspected carcinogens may require *in vitro* methods which presently suffer from such features as in appropriate bathing media due to differences in vascularity in *in vivo* and *in vitro* tests.

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TABLE 1

PENETRATION OF ENVIRONMENTAL CONTAMINANTS

Compound	Species	Application site	Solvent	Penetration parameter	Methods	Comment	References
Solvents							
Phenol	human	dermal chamber	vaporize	48%, 8 hr	--	--	55
Phenol	human	hand	water	23%, 1 hr	urinary excretion	--	56
Phenol	hairless mouse	abdomen	water	19.7 x 10^3 cm/hr	in vitro	36 days old	57
Phenol	hairless mouse	abdomen	water	28.4 x 10^3 cm/hr	in vitro	92 days old	57
Phenol	hairless mouse	abdomen	water	16 x 10^3 cm/hr	in vitro	340 days old	57
Phenol	hairless mouse	dorsal	water	20.7 x 10^3 cm/hr	in vitro	36 days old	57
Phenol	hairless mouse	dorsal	water	25.4 x 10^3 cm/hr	in vitro	92 days old	57
Phenol	hairless mouse	dorsal	water	18.3 x 10^3 cm/hr	in vitro	340 days old	57
Methanol	hairless mouse	abdomen	water	2.1 x 10^3 cm/hr	in vitro	36 days old	57
Methanol	hairless mouse	abdomen	water	3.4 x 10^3 cm/hr	in vitro	92 days old	57
Methanol	hairless mouse	abdomen	water	2.2 x 10^3 cm/hr	in vitro	340 days old	57
Methanol	hairless mouse	dorsal	water	2.7 x 10^3 cm/hr	in vitro	36 days old	57
Methanol	hairless mouse	dorsal	water	2.9 x 10^3 cm/hr	in vitro	92 days old	57

TABLE 1 - continued

Compound	Species	Application site	Solvent	Penetration parameter	Methods	Comments	References
Methanol	hairless mouse	dorsal	water	2.7×10^3 cm/hr	*in vitro*	340 days old	57
Benzene	monkey	forearm	none	0.2%, 5 days	excretion analysis	--	58
Benzene	monkey	forearm	petroleum distillate	0.1%, 5 days	excretion analysis	--	58
Hexachloro-benzene	rat	oral	cotton seed oil	5%, 96 hr	g.i. content	--	59
Metal derivatives							
Zn pyridine-thione	monkey	scalp	lotion	4%, 72 hr	excretion analysis	--	60
Pb acetate	human	forehead	lotion	0.3%, 48 hr	excretion analysis	--	61
Chromium	human	forearm	water	23%, 1 hr	patch	--	62
$CrCl_3$	guinea pig	back	water	2%, 5 hr	patch	--	63
Na_2CrO_4	guinea pig	back	water	2%, 5 hr	patch	--	63
$Na_2Cr_2O_7$	guinea pig	back	water	< 1%, 5 hr	patch	--	63
$CoCl_2$	guinea pig	back	water	< 1%, 5 hr	patch	--	63
$ZnCl_2$	guinea pig	back	water	< 1%, 5 hr	patch	--	63

TABLE 1 - continued

Compound	Species	Application site	Solvent	Penetration parameter	Methods	Comments	References
$AgNO_3$	guinea pig	back	water	< 1%, 5 hr	patch	--	63
$CdCl_2$	guinea pig	back	water	2%, 5 hr	patch	--	63
$HgCl_2$	guinea pig	back	water	< 1%, 5 hr	patch	--	63
K_2HgI_4	guinea pig	back	water	3%, 5 hr	patch	--	63
Pesticides							
Azinphosmethyl	human	forearm	acetone	16%, 5 days	excretion analysis	--	64
Monocrotophos	human	forearm	acetone	15%, 5 days	excretion analysis	--	64
Ethion	human	forearm	acetone	3%, 5 days	excretion analysis	--	64
Malathion	human	forearm	acetone	8%, 5 days	excretion analysis	--	64
Parathion	human	forearm	acetone	10%, 5 days	excretion analysis	--	64
Propoxur	human	forearm	acetone	20%, 5 days	excretion analysis	--	64
Carbaryl	human	forearm	acetone	74%, 5 days	excretion analysis	--	64

TABLE 1 - continued

Compound	Species	Application site	Solvent	Penetration parameter	Methods	Comments	References
Aldrin	human	forearm	acetone	8%, 5 days	excretion analysis	--	64
Dieldrin	human	forearm	acetone	8%, 5 days	excretion analysis	--	64
Lindane	human	forearm	acetone	9%, 5 days	excretion analysis	--	64
2,4-D	human	forearm	acetone	6%, 5 days	excretion analysis	--	64
Diquat	human	forearm	acetone	< 1%, 5 days	excretion analysis	--	64
Captan	human	field	em.c.	39 mg h-1/person	excretion analysis	--	65
Benomyl	human	field	em.c.	5 mg h-1/person	excretion analysis	--	65
Permethrin	rat	back	em.c.	$k=0.238\ (hr^{-1})$	patch	--	66
Permethrin	rat	back	dust	$k=0.067\ (hr^{-1})$	patch	--	66
Methoxychlor	goat	back	dichloromethane	20%, 72 hrs	patch	--	67
EPN	chicken	oral	capsule	91%, 2 days	g.i. content	--	68
Lindane	rat	intestine	bile	47%, 30 min	intestinal loop	--	69

TABLE 1 - continued

Compound	Species	Application site	Solvent	Penetration parameter	Methods	Comments	References
DDT	rat	intestine	bile	2%, 30 min	intestinal loop	--	69
Lindane	rat	oral	cotton seed oil	5%, 96 hrs	g.i. content	--	69
Carbaryl	rat	oral	EtOH	84%, 24 hrs	g.i. content	--	70
Carbaryl	rat	oral, ligature	EtOH	51%, 24 hrs	g.i. content	--	70
Leptophos	chicken	comb	acetone	35%, 20 days	g.i. content	--	71
2,4,5-T	rat	back	acetone	58%, 24 hrs	g.i. content	--	18
Diazinon	mouse	oral	emulfor	69%, 1 hr	g.i. content	--	27
Malathion	mouse	oral	emulfor	89%, 1 hr	g.i. content	--	27
Parathion	mouse	oral	emulfor	57%, 1 hr	g.i. content	--	27
Chlorpyrifos	mouse	oral	emulfor	47%, 1 hr	g.i. content	--	27
Propoxur	mouse	oral	emulfor	74%, 1 hr	g.i. content	--	27
Carbofuran	mouse	oral	emulfor	67%, 1 hr	g.i. content	--	27
Carbaryl	mouse	oral	emulfor	69%, 1 hr	g.i. content	--	27
Lindane	mouse	oral	emulfor	71%, 1 hr	g.i. content	--	27
Dieldrin	mouse	oral	emulfor	63%, 1 hr	g.i. content	--	27

TABLE 1 - continued

Compound	Species	Application site	Solvent	Penetration parameter	Methods	Comments	References
DDT	mouse	oral	emulfor	55%, 1 hr	g.i. content	--	27
Nicotine	mouse	oral	emulfor	83%, 1 hr	g.i. content	--	27
Permethrin	mouse	oral	emulfor	39%, 1 hr	g.i. content	--	27
Carbaryl	mouse	dermal	acetone	72%, 1 hr	patch	--	19
Methomyl	mouse	dermal	acetone	85%, 1 hr	patch	--	19
Carbofuran	mouse	dermal	acetone	76%, 1 hr	patch	--	19
Parathion	mouse	dermal	acetone	32%, 1 hr	patch	--	19
Malathion	mouse	dermal	acetone	25%, 1 hr	patch	--	19
Chlorpyrifos	mouse	dermal	acetone	69%, 1 hr	patch	--	19
Nicotine	mouse	dermal	acetone	72%, 1 hr	patch	--	19
Permethrin	mouse	dermal	acetone	80%, 1 hr	patch	--	19
DDT	mouse	dermal	acetone	34%, 1 hr	patch	--	19
Dieldrin	mouse	dermal	acetone	34%, 1 hr	patch	--	19
Chlordecone	mouse	dermal	acetone	54%, 1 hr	patch	--	19
Carbofuran	rat	oral		86%, 8 hr	g.i. content	--	72

TABLE 1 - continued

Compound	Species	Application site	Solvent	Penetration parameter	Methods	Comments	References
Parathion	mouse	dermal	none	1.4%, 1 hr	excretion analysis	--	73
Malathion	mouse	dermal	none	1.4%, 11 hr	excretion analysis	--	73
DFP	mouse	dermal	none	3.5%, 1 hr	excretion analysis	--	73
Dyfonate	rat	oral	sunflower oil	> 95%, 4 days	tissue content	--	74
Parathion	rat	dermal	acetone	59%, 5 days	patch	--	75
Carbaryl	rat	dermal	acetone	58%, 7 days	patch	--	75
Triadimefon	rat	dermal	acetone	53%, 8 days	patch	--	17
Triadimefon	rat, young	dermal	acetone	57%, 8 days	patch	--	17
Parathion	roach	dermal	acetone	14%, 1 hr	patch	--	76
	hornworm	dermal	acetone	8%, 1 hr	patch	--	76
	quail	dermal	acetone	40%, 1 hr	patch	--	76
	frog	dermal	acetone	33%, 1 hr	patch	--	76
Carbaryl	roach	dermal	acetone	15%, 1 hr	patch	--	76
	hornworm	dermal	acetone	13%, 1 hr	patch	--	76
	quail	dermal	acetone	29%, 1 hr	patch	--	76
	frog	dermal	acetone	84%, 1 hr	patch	--	76

TABLE 1 - continued

Compound	Species	Application site	Solvent	Penetration parameter	Methods	Comments	References
DDT	roach	dermal	acetone	15%, 1 hr	patch	--	76
	hornworm	dermal	acetone	5%, 1 hr	patch	--	76
	quail	dermal	acetone	22%, 1 hr	patch	--	76
	frog	dermal	acetone	13%, 1 hr	patch	--	76
Dieldrin	roach	dermal	acetone	17%, 1 hr	patch	--	76
	hornworm	dermal	acetone	3%, 1 hr	patch	--	76
	quail	dermal	acetone	22%, 1 hr	patch	--	76
	frog	dermal	acetone	13%, 1 hr	patch	--	76
Permethrin	roach	dermal	acetone	24%, 1 hr	patch	--	76
	hornworm	dermal	acetone	15%, 1 hr	patch	--	76
	frog	dermal	acetone	20%, 1 hr	patch	--	76
2,4-D	mouse	dermal	acetone	21%, 24 hr	patch	--	41
Fenvalerate	mouse	dermal	acetone	9%, 2 hr	patch	--	41
Captan	mouse	dermal	acetone	8%, 24 hr	patch	--	41
Paraquat	mouse	dermal	water	7%, 24 hr	patch	--	41
Cyhexatin	mouse	dermal	chloroform	6%, 24 hr	patch	--	41
Maleic hydrazide	mouse	dermal	acetone	5%, 24 hr	patch	--	41

TABLE 1 - continued

Compound	Species	Application site	Solvent	Penetration parameter	Methods	Comment	References
Miscellaneous							
Tris (TBPP)	human	pajamas	none	0%, 7 nights	urinary analysis	--	77
Tris	rabbit	back	none	17%, 96 hr	urinary analysis	--	78
Surfactants							
Dialkyldimethyl-ammonium chloride	rabbit	back	acetone	1%, 72 hrs	patch	--	90
Alkylbenzene sulfonate	rat	back	water	< 1%, 72 hrs	patch	--	90
	rabbit	back	water	3%, 72 hrs	patch	--	90
	guinea pig	back	water	< 1%, 72 hrs	patch	--	90
	human	back	water	1%, 144 hrs	urinary excretion	--	90
Dodecyl dimethyl-amine oxide	rat	back	water	40%, 72 hrs	patch	--	90
	mouse	back	water	46%, 72 hrs	patch	--	90
	rabbit	back	water	55%, 72 hrs	patch	--	90
1 to 6 substituted Cl's on PCB	rat	fed	--	> 90%, 4 days	intestinal excretion	--	91
TCDF	guinea pig	gavage	emulfor	94%, 4 days	tissue content	--	92

TABLE 1 - continued

Compound	Species	Application site	Solvent	Penetration parameter	Methods	Comments	References
PCB-hexachlor	rat	intestine	bile	1%, 30 min	intestinal loop	--	69
Aflatoxin	rat	back	DM50	None detected 24 hrs	organ levels	--	88
Aflatoxin	rat	back	acetone	ND, 24 hrs	organ levels	--	88
2,4-toluene-diamine	monkey	abdomen	acetone	54%, 5 days	excretion analysis	--	89
	human	forearm	acetone	24%, 5 days	excretion analysis	--	89
2-nitrophenyl-anidiamine	monkey	forearm	acetone	30%, 5 days	excretion analysis	--	89
	pig	back	acetone	18%, 5 days	excretion analysis	--	89
N-nitrodiethanol amine	monkey	abdomen	acetone	34%, 5 days	excretion analysis	--	89
	pig	back	acetone	12%, 5 days	excretion analysis	--	89
2,4-diamino anisole	monkey	abdomen	acetone	5%, 5 days	excretion analysis	--	89
	human	forearm	acetone	4%, 5 days	excretion analysis	--	89
p-dioxane	monkey	forearm	MeOH	2%, 5 days	excretion analysis	--	89
Alkyl ethoxylate	rat	oral	water	90%, 72 hrs	g.i. tract	--	90
	rat	back	water	48%, 72 hrs	patch	--	90

TABLE 1 - continued

Compound	Species	Application site	Solvent	Penetration parameter	Methods	Comments	References
Hexachlorophene	rat	back	DMSO	45%, 24 hrs	patch	--	84
Hexachlorophene	rat	back	acetone	73%, 24 hrs	patch	--	84
Hexachlorophene	rat	back	acetone	82%, 24 hrs	patch	--	84
Hexachlorophene	human	back	propylene glycol	10ng/cm^2/hr	in vitro	--	85
Hexachlorophene	rat	back	none	77%, 15 days	patch	--	86
	rat weanling	back	none	53%, 24 hrs	patch	--	86
	guinea pig	back	none	67%, 5 days	patch	--	86
Hexachlorophene	pig weanling	back	none	18%, 5 days	urinary excretion	--	86
Hexachlorophene	guinea pig	back	none	93%, 24 hrs	patch	--	87
Hexachlorobenzene	rat	intestine	bile	10%, 30 min	intestinal loop	--	69
PCB-trichlor	rat	intestine	bile	8%, 30 min	intestinal loop	--	69
PCB-pentachlor	rat	intestine	bile	3%, 30 min	intestinal loop	--	69

TABLE 1 - continued

Compound	Species	Application site	Solvent	Penetration parameter	Methods	Comments	References
TCDD	rat	oral	EtOH	16%, 24 hr	liver uptake	absorbed on soil particles, 8 days	82
TCDD	rat	oral	EtOH	< 0.1%, 24 hr	liver uptake	absorbed on activated C	82
TCDD	rat	back	MeOH	15%, 24 hr	liver uptake	--	82
TCDD	rat	back	MeOH	2%, 24 hr	liver uptake	absorbed on soil particles, 8 days	82
TCDD	rat	back	MeOH	< 0.1%, 24 hr	liver uptake	absorbed on activated C	82
Chloramphenicol	hairless mouse	*in vitro*	propylene glycol	3×10^{-4} cm/min^{-1}	*in vitro*	--	83
Hexachlorophene	rat	back	EtOH	75%, 24 hrs	patch	--	84
Hexachlorophene	rat	back	corn oil	66%, 24 hrs	patch	--	84
Hexachlorophene	rat	back	Na lauryl SO_4	71%, 24 hrs	patch	--	84

TABLE 1 - continued

Compound	Species	Application site	Solvent	Penetration parameter	Methods	Comments	References
PNA	rat	gavage	emulfor	> 95%, 3 days	tissue content	--	93
TBBC	rat	gavage	emulfor	13%, 3 days	tissue content	--	94
TCDF	rat	gavage	emulfor	90%, 3 days	tissue content	--	95
HBN	rat	gavage	emulfor	60%, 3 days	tissue content	--	96
Tetrachloro-ethylene	rat	drinking water	water	> 96%, 24 hrs	tissue content	--	97
Benzidine	rat	dermal	acetone	51%, 24 hrs	patch	--	98
Dimethoxy-benzidine	rat	dermal	acetone	28%, 24 hrs	patch	--	98
Dichlorobenzine	rat	dermal	acetone	49%, 24 hrs	patch	--	98
Polymethylated methacrylate	rat	oral	none	12%, 8 days	g.i. tract	--	79
Nitrosoproline	rat	oral	none	98%, 7 days	g.i. tract	--	80
Alkylpoly-ethoxylate	rat	back	water	25%, 4 days	patch	--	81
TCDD	rat	oral	EtOH	37%, 24 hr	liver uptake	--	82

TABLE 2.

EFFECT OF ANATOMICAL SITE OF APPLICATION ON PENETRATION*

	Percent absorbed		
Anatomical Site	Monkey (testosterone)	Man (parathion)	Mouse (parathion)
Ventral forearm	8.8	8.6	
Chest	5.3		
Cheek	9.6		
Scalp	20.4	32.2	
Vagina	63.1		
Hind feet			30.3
Front feet			30.3
Nose			81.6
Testicle			37.0
Tail			28.0
Palm		11.8	
Foot, ball		13.5	
Abdomen		18.5	
Hand, dorsum		21.0	
Jaw		33.9	
Forehead		36.3	
Axilla		64.0	
Scrotum		101.6	

*Data taken from Reference 104, 142, 143